REMARKS

This Amendment and Remarks are filed in response to the Office Action dated October 16, 2007 wherein claims 31-42 and 45 stand rejected. Claims 43 and 44 are withdrawn from consideration.

Double Patenting

Claims 31-42 and 45 are rejected on the ground of double patenting.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e,g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046,29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Omum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438,164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528,163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 31-42 and 45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16-20 of copending Application No. 11/126,863 (published as US 2005/0249774). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a method for treatment of migraine, migraine headache, nausea, and vomiting associated with chemotherapy, radiotherapy, surgery, pregnancy, pre-menstrual syndrome, menstruation or menopause, with the aid of an intravaginal delivery device comprising administering said intravaginal device and a composition comprising an anti-migraine or anti-nausea drug, a mucoadhesive agent, a lipophilic or hydrophilic carrier, and a sorption promoter. Many of the anti-migraine or anti-nausea drugs, mucoadhesive agents, lipophilic or hydrophilic carriers, sorption promoters and delivery devices are overlapping in scope, and some are identical (i.e. naratriptan, HPMC, saturated mono-, di-, or triglyceride of fatty acids having 8 to 18 carbons, PEG 6000/PEG 1500, ethoxydiglycol, and tampon, respectively). Therefore, the scope of the copending applications is overlapping, and thus they are obvious variants of one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants disagree with the double patenting rejections because the claims in the 11/126,863 application are directed to the vaginal device and not to the method for treatment, however, to advance the examination Applicants submit herewith a fully executed Terminal Disclaimer disclaiming the provisionally rejected claims over the co-pending application Ser. No. 11/126,863.

Claims 31-42 and 45 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 13, 15-20 and 22-23 of U.S. Patent No. 6,197,327 (hereinafter Harrison et al. '327), in view of U.S. Patent No. 6.255.502 (hereinafter Penkler et al.). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an intravaginal drug delivery system containing an appropriate pharmaceutical agent incorporated into a pharmaceutically acceptable carrier, mucoadhesive agent, and sorption promoter, whereby the pharmaceutical agent is released into the vagina and absorbed through the vaginal mucosa. Many of the pharmaceutical agents, mucoadhesive agents, lipophilic or hydrophilic carriers, sorption promoters and delivery devices are overlapping in scope, and some are identical (i.e. ketorolac, HPMC, saturated mono-, di-, or triglyceride of fatty acids having 8 to 18 carbons, PEG 6000/PEG 1500, ethoxydiglycol, and tampon, respectively).

Harrison et al. '327 do not claim the pharmaceutical agent to comprise naratriptan. However, Penkler et 211. teach naratriptan, sumatriptan and almotriptan as suitable agents for the treatment of migraines (column 7, lines 42-47; column 10, lines 47 -48; and claims 1, 8) through vaginal administration (column 13, lines 4-5 and 8).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time of the instant invention to use naratriptan as the pharmaceutical agent in the vaginal delivery device of Harrison et al. '327, because Penkler et al. teach that naratriptan can be applied via the vagina for treatment of migraines.

Applicants disagree. Harrison's claims are directed to transvaginal delivery of a pharmaceutically active agent into uterus, myometrium or endometrium for treatment of dysmenorrhea rather than delivery to the systemic circulation for treatment of migraine and/or nausea, as claimed herein. However, to overcome the double patenting rejection, Applicants submit the fully Executed Terminal Disclaimer.

With submission of Terminal Disclaimers both double patenting rejections are overcome.

Rejections under 35 USC 102

Claims 31-35 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,086,909 (hereinafter Harrison et al. (909).

Harrison et al. '909 disclose a method for treatment of dysmenorrhea comprising an intravaginal drug delivery system containing an appropriate pharmaceutical agent incorporated into

a pharmaceutically acceptable carrier whereby the pharmaceutical agent is released into the vagina and absorbed through the vaginal mucosa to provide relief of dysmenorrheal (abstract). Harrison et al. '909 further disclose the pharmaceutical agent to comprise aspirin, ibuprofen, ketorolac and naproxen (column 7, lines 51-53; claim 20), and the pharmaceutically acceptable carrier comprises a hydrophilic or hydrophobic carrier, such as semi-synthetic glycerides of saturated fatty acids with 8 to 18 carbons and PEG 6000/1500, respectively (column 8, lines 8-15). Also, Harrison et al. '909 disclose the pharmaceutical formulations further comprising a mucoadhesive agent, preferably hydroxypropyl methylcellulose (column 8, lines 16-22), and a penetration enhancer, preferably ethoxydiglycol (column 8, lines 23-28). Harrison et al. '909 also disclose the method of applying the pharmaceutical formulation with the aid of an intravaginal delivery device, such as tampon device, vaginal ring, pessary, tablet, vaginal suppository, vaginal sponge, bioadhesive tablet, bioadhesive microparticle, cream, lotion, foam, ointment, solution and gel (column 2, lines 37-43; column :3, lines 8-67; column 4, lines 1-27; and column 9, line 4 through column 13, line 67). Harrison et al. '909 also disclose that preferred formulations for hydrophilic drugs comprise between about 60-90% by weight lipophilic carrier, between about 5-25% mucoadhesive agent, and between about 5-20% sorption promoter, whereas preferred formulations for lipophilic drugs comprise between about 50-90% by weight hydrophilic carrier, between about 5-20% mucoadhesive agent, and between about 5-25% sorption promoter (column 8, lines 31-34 and 44-47).

Applicants disagree. Anticipation requires that the prior art reference describes the complete invention and that both the rejected invention and the anticipating invention are the same. In this case, it is not so, particularly in view of the amended claims.

Harrison reference is directed to treatment of dysmenorrhea by delivering certain groups of analgesic and other drugs intra and transvaginally to the to vagina and through the vagina to uterus, myometrium, endometrium, and to the uterine muscle responsible for dysmenorrheal pain.

Examiner will note that anatomically, uterus, myometrium and endometrium are located in a very close vicinity of vagina. Therefore, the transport of the drugs across vaginal mucosa to the uterus in amount needed for treatment of dysmenorrheal pain is achieved primarily by delivering a needed amount of the drug to the vicinity of the vaginal mucosa, by providing means for adhering a composition comprising the drug to the vaginal mucosa and providing means for transport through the vaginal mucosa into uterus. The adhesion and transport of the drug through the vaginal mucosa directly to the targeted uterus is achieved by appropriate combination of the mucoadhesive agent and penetration enhancer present in concentrations that are appropriate for each individual drug characteristic.

The aim of the Harrison is to deliver the needed amount of the drug to uterus but limit the concentration of the drug in the systemic circulation. Systemic delivery is described by Harrison as being undesirable for treatment of dysmenorrhea.

A reason for this is that the dysmenorrheal pain originates in the uterus and the drug needs to be delivered to the uterus in an amount that eliminated or decreases the pain. This is the first and foremost distinction between the instant invention and the Harrison reference.

The origin of pain for treatment of dysmenorrhea is in the uterus that is anatomically located close to the vagina. The origin of the migraine or nausea is in the brain, anatomically very remote organ from the vagina.

As described amply in Harrison' specification, systemic administration of analgesic drug, generally by the oral route, to the patient, has not successfully relieved the conditions in many women and such administration of systemically delivered drugs leads to severe secondary symptoms due to large doses needed to achieve a relief. This failure is believed to be a result of a failure of oral administration to deliver to and achieve an efficacious dosage level of the analgesic in the uterine muscle. As described by Harrison, to achieve the efficacious levels of the drug in the uterus by systemic administration requires a very large systemic concentration of the drug in order for the needed amount to reach the targeted area, that is the uterus.

Harrison's method overcomes prior problems observed with drug delivery to the uterus, myometrium and endometrium.

On the other hand, in the instant invention, the disease or condition is such that while the systemic treatment is needed to deliver the drug to the brain to treat or prevent migraine and/or nausea, such treatment is prevented by the condition itself. Nausea, that invariably accompanies migraine, prevents oral

systemic delivery of the drugs suitable for treatment of migraine. The treated condition, i.e. nausea, thus prevents delivery of anti-migraine and anti-nausea drugs into systemic circulation, particularly so in amounts of drug needed to treat the migraine spasm or vomiting.

Contrary to the Harrison treatment where the amount in the systemic circulation is minimized or eliminated altogether, the instant method provides for large doses of the drug delivered into the systemic circulation in order to provide relief from the migraine pain or vomiting by bypassing the gastrointestinal tract.

In order to achieve this, the anti-migraine and anti-nausea drugs, claimed herein, are formulated into a composition that provides means for fast transport of the said drug directly into the systemic circulation. Such release is achieved by varying ratios of various components of the transvaginal composition and depends on the chemical and chemico-physical properties of the drug itself. The resulting composition is then incorporated into the device or into a coating of the vaginal device.

The variability of the drugs (analgesics versus anti-migraine or anti-nausea), treatments (dysmenorrhea versus migraine and nausea), targeted delivery sites (uterus versus brain) and formulations (strongly mucoadhesive composition with short transport to uterus with minimized systemic delivery versus delivery of the drug specifically to the systemic circulation) clearly distinguishes two inventions.

Applicants amended claims to be directed solely to anti-migraine and anti-nausea drugs and canceled any other drug that could be used for treatment of dysmenorrhea.

Applicants respectfully submit that the instant claims are not anticipated by Harrison and request that the rejection is withdrawn.

Claims 31-35 are rejected under 35 U.S.C.102(b) as being anticipated by Harrison et al. '327.

Harrison et al. '327 disclose for treatment of dysmenorrhea comprise an intravaginal drug delivery system containing an appropriate pharmaceutical agent incorporated into a pharmaceutically acceptable carrier whereby the pharmaceutical agent is released into the vagina and absorbed through the vaginal mucosa to provide relief of dysmenorrheal (abstract). Harrison et al. '327 further disclose the pharmaceutical agent to comprise aspirin, ibuprofen, ketorolac and naproxen (column 6, lines 30 and 32; claims 3, 10, 13, 16, 18 and 22), and the pharmaceutically acceptable carrier comprises a hydrophilic or hydrophobic carrier, such as semi-synthetic glycerides of saturated fatty acids with 8 to 18 carbons and PEG 6000/1500, respectively (column 6, lines 52-60). Also, Harrison et al., 211. '327 disclose the pharmaceutical formulations further comprising a mucoadhesive agent, preferably hydroxypropyl methylcellulose (column E3, lines 61-67; and claim 6), and a penetration enhancer, preferably ethoxydiglycol (column 7, lines 1-8; and claim 7). Harrison et 211. '327 also disclose the method of applying the pharmaceutical formulation with the aid of an intravaginal delivery device, such as tampon device, vaginal

ring, pessary, tablet, vaginal suppository, vaginal sponge, bioadhesive tablet, bioadhesive microparticle, cream, lotion, foam, ointment, solution and gel (column 7, line 51 through column 12, line 20). Harrison et al. '327 also disclose that preferred formulations for hydrophilic drugs comprise between about 60-90% by weight lipophilic carrier, between about 5- 25% mucoadhesive agent, and between about 5-20% sorption promoter, whereas preferred formulations for lipophilic drugs comprise between about 50-90% by weight hydrophilic carrier, between about 5-20%> mucoadhesive agent, and between about 5- 25% sorption promoter (column 7, lines 9-12 and 22-25; and claim 8).

Applicants disagree. The same arguments as advanced above are appropriate to this rejection. Applicants amended claims to eliminate drugs that are claimed by Harrison. The method for treatment, drugs and the diseases or conditions are different.

The instant claims are not anticipated by Harrison '337. Rejection should be withdrawn. It is so respectfully requested.

Rejections under 35 USC 103

Claims 31-42 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrison et al. '909 in view of Penkler et al.

Applicants claim a method for treatment of migraine, migraine headache, nausea, and vomiting associated with chemotherapy, radiotherapy, surgery, pregnancy, pre-menstrual syndrome, menstruation or menopause, with the aid of an intravaginal delivery device comprising administering said intravaginal device and a composition comprising naratriptan, a mucoadhesive agent (i.e. HPMC), a lipophilic or hydrophilic

carrier (mono-, di-, or triglyceride of fatty adds with 8 to 18 carbons or PEG 6000/1500, respectively), and a sorption promoter (ethoxydiglycol).

Examiner argues that Harrison et al. '909 teach a an intravaginal drug delivery system containing an appropriate pharmaceutical agent incorporated into a pharmaceutically acceptable carrier whereby the pharmaceutical agent is released into the vagina and absorbed through the vaginal mucosa, as discussed above.

Examiner admits that Harrison et al. '909 do not teach the pharmaceutical agent to comprise naratriptan. However, Penkler et al. teach naratriptan, sumatriptan and almotriptan as suitable agents for the treatment of migraines (column 7, lines 42-47; column 10, lines 47-48; and claims 1, 8) through vaginal administration (column 13, lines 4-5 and 8).

Therefore, Examiner finds that it would have been prima facie obvious for one skilled in the art at the time of the instant invention to use naratriptan as the pharmaceutical agent in the intravaginal delivery device of Harrison et al. '909, because Penkler et al. teach that naratriptan can be applied via the vagina for treatment of migraines.

Examiner concludes that from the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the

references, especially in the absence of evidence to the contrary.

Applicants disagree. The Harrison reference and its relevance to the instant invention was discussed above. Applicants respectfully submit that Examiner is interpreting th Penkler reference incorrectly and that a combination of the two references do not make the instant invention obvious or prima facie obvious.

Penkler reference teaches pharmaceutical composition for enhancing permeation of basic drugs across the skin, which is a keratinized epithelial barrier, and non-keratinized epithelial barriers, including the nasal, rectal, and vaginal mucosa. Applicants acknowledge that Penkler lists anti-migraine drugs such as naratriptan and sumatriptan as suitable active ingredients for treatment of migraine and also that the drugs are suitable for transdermal or transmucosal delivery, including through vaginal administration (column 13, lines 4-5 and 8), according to Penkler method. However, such delivery is limited by the conditions imposed by Penkler's method.

Examiner makes the rejection to be the prima facie obviousness without considering what properties and conditions are needed for Penkler formulation to achieve the transdermal or transmucosal delivery of the anti-migraine drugs.

The drugs formulated for transdermal or transmucosal delivery disclosed by Penkler are limited to drugs that exist in a positively charged sale form (acid addition salts). Such delivery is only successful when such positively charged drug is in combination with a negatively charged fatty acid or bile acid

(column 1, lines 11-13, column 4, lines 41-43, claims 1, 4 & 6). Therefore, the teaching by Penkler mandates formation of a neutral species by electrostatic attraction between oppositely charged ions that is known to one ordinary skilled in the art as "ion-pairing".

Various applications of successful improvement of transdermal and transepithelial delivery of therapeutic agents using "ion-pairing" have been described in the scientific literature (e.g., "Applications of the ion-pair concept to hydrophilic substances with special emphasis on peptides" by Quintanar-Guerrero et al., (1997), *Pharm. Res.*, 14;119-127 (Copy enclosed for Examiner convenience).

None of those limitations is applicable to the method and composition disclosed in the present invention. The present invention provides a combination of a therapeutically appropriate agent such as an anti-migraine and/or anti-nausea drug with a mucoadhesive composition comprising an inert hydrophilic or lipophilic carrier and a non-ionizable sorption promoter.

Inclusion of the chemically narrowly defined glycol ether or ester as sorption promoter further distinguishes the present invention from Penkler reference that specifically requires incorporation of negatively charged fatty and bile acids as penetration enhancers in order to achieve desired electrostatic interaction for ion-pairing (column 11, lines 8-13).

To compensate for compromised aqueous solubility of the ion-pair resulting from neutralized charge distribution between the counter (positive/negative) ions and the presence of a hydrophobic alkyl chain or rigid sterol moiety of the fatty and

bile acids, respectively, Penkler teaches a composition containing hydrophilic cyclodestrine (column 11, lines 37-51). These natural cyclic oligosaccharides form inclusion complexes with the ion-paired drug and increase membrane permeation of the lipophilic ion-pair by modulating the aqueous boundary layer of the epithelial barrier (see "Effects of cyclodestrins on drug delivery through biological membranes" by Loftsson et al., *J. Pharm. Sci.*, (2007) 96:2532-2546 (Copy enclosed).

In contrast, the instant application does not involve or suggest a method or means to form ion-paired complexes or to increase or enhance aqueous solubility using hydrophilic cyclic oligosaccharides in order to facilitate drug permeation across the vaginal mucosa.

The Applicants wish to emphasize that the same pharmaceutical excipient may serve different roles in different composition despite its identical chemical structure. However, it is relevant to notice and for Examiner to consider that performance functionalities of such excipients critically depend on physicochemical properties of the agent under defined physiological conditions at the site of administration.

The composition of this invention requires the presence of non-ionizable glycol ether/ester derivative acting as penetration enhancers to disrupt important regulatory proteins at cell-cell connections and to perturb the bilayer environment of the vaginal epithelium. As a consequence of these excipient-induced alterations of the physiochemical properties of the biological barrier the incorporated anti-migraine/anti-nausea drug

efficiently permeates across the membrane into the systemic circulation and is able to reach the target site in the brain.

Unique to the vaginal environment is a significantly more acid pH that affects viscosity of mucoadhesive agents. Therefore, the compositions disclosed by the applicant are restricted to limiting mixtures of selected excipients that create, in the physiological environment of the vaginal cavity the optimal physiochemical conditions for the glycol ether/ester derivatives to alter the mucosal barrier properties for improved drug delivery.

Penkler discloses composition using chemically related excipients without restrictions for the tissue it is to be applied to. For example for buccal, sublingual, or nasal administration (column 12, lines 16-43), no regard is given to pH value. As the mucosal pH value of all those claimed sites of administration is significantly greater (pH 6.7-7.5) than in the vaginal cavity, the chemical composition of epithelial cells dramatically varies (e.g., water:protein:lipid ratio). Additionally, and the anatomical barrier consists of only 2-3 cell layers as compared to 20-30 layers as in the vaginal mucosa. For these reasons, a person skilled in the art would recognize that compositions disclosed by Penkler do not comprise suitable conditions for anti-migraine/anti-nausea drugs to efficiently permeate the vaginal mucosa.

Moreover, Penkler supports this conclusion by limiting vaginal administration of the acid addition salt of the water-soluble cyclodextrin inclusion complex to convention pessary

formulations without mucoadhesive agent or sorption promoter (column 12, lines 48-51).

Prima facie obviousness rejection is based on combination of Harrison and Penkler references.

As already discussed above in 102 rejections, Harrison et al., ('327) teaches methods and composition for the treatment of dysmenorrhea. Because the site of administration of those compositions disclosed in this patent is also the vaginal cavity, the list of pharmaceutically acceptable excipients comprises similar inactive carrier materials to prepare conventional vaginal devices, including tampons, suppositories, films, foam, and tablets.

In the assessment of relevant prior art, however, it is essential to distinguish the important physiological change in environmental pH that occurs during menstruation, the time when dysmenorrhea occurs. Normally, the environmental pH value in the vaginal cavity is around pH 4-5 as a consequence of acidic secretions from commensal vaginal microflora. Following the scientific concept of pH partition theory (Penkler, column 1, line 54) the increase in vaginal pH during menstruation from pH value 4-5 to about 7.4 due to the presence of blood can dramatically change the lipophilic properties of an ionizable drug molecule and, consequently, requires different compositions for effective transmucosal drug delivery.

Other relevant changes in the epithelial barrier of the vagina during menstruation include reduced thickness due to altered steroid hormone levels and increased paracellular permeability due to pH-induced modulation of protein-protein

interactions at the tight junctions. As a consequence of those physiological changes, it is not obvious to a person of ordinary skill in the art how to substitute one component with a known function as disclosed by Harrison. Importantly, the therapeutic focus of the disclosed methods and composition in the Harrison patent is unambiguously the uterine muscle (column 1, line 40).

In contrast to the present invention where the composition is designed to maximize transmucosal delivery of drugs into the systemic circulation, the therapeutic advantage of the invention disclosed by Harrison et al., is clearly limited to maximize the deposition of a drug following vaginal administration in the uterine muscle while minimizing systemic drug concentrations that are usually associated with severe side effects (column 5, line 65). For the person of ordinary skill in the art, this clearly separates the two inventions, with Harrison et al. disclosing methods and compositions for local or topical drug delivery, whereas the present invention distinctly centers on methods and compositions suitable for systemic drug delivery.

Taking into consideration all variables required by Penkler and Harrison for achieving the transvaginal drug delivery of the anti-migraine or anti-nausea drug, when this drug, present in its acid additional salt form, would be formulated using the mucoadhesive composition of Harrison directed to targeted drug delivery to the uterus, myometrium or endometrium, such formulation (if the acid addition salt of the anti-migraine drug could be formulated according to Harrison) would achieve at most a targeted delivery of such drug into vagina, uterus, myometrium

or endometrium with minimal, if any, delivery to the systemic circulation.

Such drug delivery would defeat the aim and purpose of the instant invention which is to deliver systemically an efficacious amount of the anti-migraine drug to the brain while avoiding the gastrointestinal system. Additionally and noticeably, Harrison formulations are geared toward delivery during menstruation and if the invention and anti-migraine drugs were delivered during menstruation, the pH conditions of the vagina would further obscure and complicate the transvaginal delivery and would not result in the systemic delivery of these drugs and in treatment of migraine.

It is respectfully submitted that a combination of Harrison and Penkler references does not make the instant invention obvious and even more so prima facie obvious. The rejection should be withdrawn and the claims passed to issue. It is so respectfully requested.

SUMMARY

In summary, claims 31-50 are pending, claims 31 and 37 are amended and arguments are submitted to overcome Examiner's rejections. With these amendments and arguments, all rejections are overcome. Notice of Allowance is respectfully solicited.

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Respectfully submitted,
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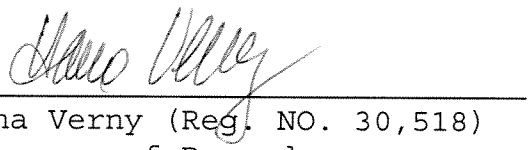

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